CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
BIFENTHRIN

Chemical Code # 2300, Tolerance # 50429
SB 950 # N/A
Original date: August 26, 1987
Revised dates: 7/9/90, 9/19/94, 4/4/00

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effects
Chronic toxicity, dog:	No data gap, no adverse effects
Oncogenicity, rat:	No data gap, no adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effects
Reproduction, rat:	No data gap, no adverse effects
Teratology, rat:	No data gap, no adverse effects
Teratology, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, no adverse effects
DNA damage:	No data gap, no adverse effects
Neurotoxicity:	No data gap, no adverse effects

Toxicology one-liners are attached.

All record numbers through 173399 were examined (Document No. 50429-231). This includes all records indexed by DPR as of 4/3/00.

In the one-liners below:

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.

File name: t20000404.doc
Revised by Aldous, 4/4/00.

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 50429-050 to 50429-056; 42408 to 42417; "Combined Chronic Oral Toxicity and Oncogenicity Study of FMC 54800 (Biphenate): 2 Year Feeding Study in Albino Rats". Sprague-Dawley rats. FMC Toxicology Laboratory; 1/31/86. Bifenthrin Technical (FMC 54800), 88.35% a.i., 98% cis, 2% trans; 200, 100, 50, 12 and 0 ppm in feed; 50/sex/dose for 2 years. No oncogenic effects. Effects included tremors, abrasions, alopecia, tail lacerations, reduced weight gain (females only) and reduced RBC 12% (males only). All effects were observed at 200 ppm. NOEL = 100 ppm; **No Adverse Effects; Study Acceptable.** (Martz, 12/29/86; Updated, 5/8/89, Morgan)

CHRONIC TOXICITY, RAT

(See Combined, above)

CHRONIC TOXICITY, DOG

** 50429:078, 112; 48262 and 75163; "52-Week Chronic Oral Toxicity Study in Dogs -- FMC Study No. A83-821."; 831; Hazleton Labs., America, Inc., Project No. 104-219; 6/17/85; FMC 54800 Technical (Bifenthrin), 89.7%, administered to 4 Beagles/sex/group at nominal concentrations of 0, 0.75, 1.50, 3.0 and 5.0 mg/kg/day in gelatin capsules for 52 weeks; Intermittent delayed onset of tremors occurring through week 29 at 3.0 and 5.0 mg/kg/day. Nominal NOEL = 1.50 mg/kg/day (tremors); **No Adverse Effects Indicated; ACCEPTABLE**. (Margolis and Gee, 10/13/88, Updated, Morgan, 3/31/89, Originally the study was unacceptable, stability analysis was submitted and reviewed, revised 8/11/89, Morgan)

ONCOGENICITY, RAT

(See Combined, above)

ONCOGENICITY, MOUSE

**** 50429:057 - 064, 112; 42418-42425, 75162;** "Oncogenicity Study in Mice (Swiss-Webster Derived, Tac(SW)fBR)"; 832; FMC Toxicology Laboratories; 2/3/86; FMC 54800 (Bifenthrin) Technical, 88.35% a.i., 98% cis, 2% trans; 50, 200, 500 and 600 ppm in feed; 50/sex/dose for 20-21 months; Tremors were observed in 1 male at 50 ppm, 2 males and 2 females at 200 ppm and among all mice at 500 and 600 ppm; NOEL = 50 ppm (tremors); **POSSIBLE ADVERSE EFFECT** Urinary bladder leiomyosarcoma (males - at 600 ppm there was a 29% incidence and the occurrence was dose-related, females - at 600 ppm there was 0% incidence); **NOAEL = 500 ppm**; **Acceptable** (Martz, 1/26/87; Updated 5/8/89, Morgan, Revised 8/11/89, Morgan, historical control data were submitted indicating the only adverse effect is Urinary bladder leiomyosarcoma).

50429-153 131602 "Oncogenicity Lifetime Feeding Study in Albino Mice Histopathological Review

of Selected Sections of Liver, Lung and Urinary Bladder"; Butler, W. H., BIBRA, UK, 7/16/91; selected slides of bladder lesions in the FMC study, record #'s 42418-42425, were re-evaluated by three pathologists; they concluded that the tumors were not leiomyosarcomas but might have been derived from vascular mesenchyme. The incidence of the submucosal bladder tumors, based on the re-evaluation by only one pathologist, was modified from the original report with 5 additional tumors reported in the controls only. As the revised incidences in male mice were not validated by all three pathologists, the re-evaluation results were judged not sufficient for a re-analysis of the tumor data. Supplementary report for 42418-42425. No worksheet. Gee, 9/19/94

REPRODUCTION, RAT

** 50429-065 - 50429-070; 42427-42432; "Multigeneration Reproduction Study with FMC 54800 (Biphenate) Technical in Rats"; 834; FMC Toxicology Laboratory; 1/31/86; Bifenthrin technical (FMC 54800), 88.35% a.i., 98% cis, 2% trans; 100, 60, 30 and 0 ppm in the feed for 8 weeks prior to F_0 mating through F_{2b} weaning; 25/sex/dose; no fertility or reproductive effects, other effects include tremors during lactation, ovary weight reduction in adults; NOEL = 100 ppm (reproductive/fertility), NOEL = 60 ppm (tremors), NOEL = 30 ppm (ovary weight reduction); **No Adverse Effects Indicated; Study Acceptable.** (Martz, 1/5/87; Updated 5/8/89, Morgan)

TERATOLOGY, RAT

** 50429-014; 36637; "Teratology Study in Rats with FMC 54800 Technical (Biphenate)"; 833; FMC Toxicology Laboratory; 2/24/84; FMC 54800 technical; 0.5, 1.0 and 2.0 mg/kg days 6-15 of gestation, by oral gavage; vehicle - corn oil; 250 mg/kg/day positive control; tremors at high dose, no developmental toxicity; Maternal NOEL = 1.0 mg/kg/day (tremors); Developmental NOEL = HDT = 2.0 mg/kg/day; **No Adverse Effects Indicated; Study Acceptable.** (Originally reviewed and found unacceptable, Aldous 12/17/85; additional data submitted and study found acceptable, Aldous 5/30/86; Updated 5/8/89, Morgan)

TERATOLOGY, RABBIT

** 50429-015; 36638; "Teratology Study in Rabbits with FMC 54800 Technical"; 833; FMC Toxicology Laboratory; 2/24/84; FMC 54800 technical; 0, 2.67, 4.0, 8.0 mg/kg days 7-19 of gestation by gavage; Vehicle - corn oil; Material effects included head and forelimb twitching at 4.0 mg/kg/day and higher; Tremors, one case of loss of muscle control and clonic convulsions (8 mg/kg), Maternal NOEL = 2.67 mg/kg/day (head and forelimb twitching); Developmental NOEL = HDT = 8 mg/kg/day; **No Adverse Effects Indicated; Study Acceptable.** (Originally reviewed and found unacceptable, Aldous 12/18/85; Additional data submitted and study found to be acceptable, Aldous 5/30/86; Updated 5/8/89, Morgan)

GENE MUTATION

** 50429-022; 36655; "Salmonella/Mammalian-Microsome Plate Incorporation Mutagenicity Assay (Ames Test)"; 842; Microbiological Associates, Bethesda, MD; 10/4/83; FMC 54800 Technical; 0-7500 ug/plate (triplicate plates), ± S9 rat liver; No increase in mutation reversion; **No Adverse Effects Indicated; Study Acceptable.** (Remsen (Gee) 12/18/85, originally found unacceptable, upgraded to acceptable based on revision in guidelines in May, 1987, Upgrade dated 5/8/89, Morgan)

50429-010; 36629; "L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay"; 842; Microbiological Associates, Bethesda, MD; 10/26/83; FMC 54800 Technical, Lot # E-2392-105, purity = 88.35% ; 4 hour exposure; Cloning phase treatment levels - without activation: 0.24, 0.18, 0.13, 0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018 µl/ml with S9 activation: 0.10, 0.075, 0.056, 0.042, 0.032, 0.024, 0.018, 0.013, 0.010, 0.0075 µl/ml; The frequency of the mutations was greater than twice the control value at treatment levels greater than 0.075 µl/ml in both the activated and non-activated tests, in each case a dose-response relationship was evident; **Possible Adverse Effect: Possible increase in mutation frequency; Study Unacceptable and not upgradeable**, No confirming experiment. (Remsen (Gee), 12/17/85; Updated 5/18/89, Morgan)

50429-010; 36630; "Mutagenicity Evaluation of FMC 54800 Technical in the Sex-linked Recessive Lethal Test in Drosophila Melanogaster"; 842; Litton Bionetics, Kensington, MD; 12/17/85; Bifenthrin Technical, purity = 88.35%; 0 (unsalted butter), 50 and 100 µg/ml; doses selected from preliminary toxicity and fertility tests; slight but not significant increased lethality in test groups; no repeat experiment; **Study Unacceptable.** (Remsen (Gee) 12/17/85; Updated 5/8/89, Morgan)

50429-010; 36633; "CHO/HGPRT Point Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation"; 842; Microbiological Associates, Bethesda, MD; 7/11/84; FMC 54800 Technical, Lot # E-2392-105, Purity = 88.3%; ± S9; 0 (vehicle), 250, 500, 750 and 1000 µg/ml for 5 hours, -S9; 0 (vehicle), 20, 30, 40, 50, for 5 hours, +S9; 9 day expression time; borderline increase in mutation frequency; no repeat trial; loss of a number of cultures; **Study Unacceptable.** (Remsen (Gee) 12/18/85; Updated 5/19/89, Morgan)

** 50429-072; 44164; "Study to Determine the Ability of FMC 54800 to Induce Mutations to 6-Thioguanine Resistance in Mouse Lymphoma, L5178Y Cells Using a Fluctuation Assay"; 842; Microtest Research, Ltd., Heslington, England; 3/86; FMC 54800, 88.35%, Lot# 2392-105; L5178Y HGPRT LOCUS ± S9 (rat liver); trial 1: 0, 15.8, 50, 158 and 500 µg/ml; trial 2: 0, 50, 100, 150 and 200 µg/ml; duplicates; fluctuation test; no biologically significant increase in MF; **No Adverse Effects Indicated; Study Acceptable.** (Remsen (Gee) 12/17/85; Updated 5/19/89, Morgan)

Summary of Gene Mutation Effects: The collective data indicate that evidence for gene mutation is equivocal. No adverse effect is indicated at this time.

CHROMOSOME EFFECTS

** 50429-010; 36631; "Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells"; 843; Microbiological Associates, Bethesda, MD; 1/5/84; FMC 54800 Technical, Lot # E2392-105, purity = 88.35%; Chinese hamster ovary cells were exposed with and without rat liver activation , 0-10,000 µg/ml for 2 hours(+S9) or 16 hours (-S9) plus 3 hours at colchicine, toxicity measured also; single time of harvest;

no increase in aberrations/100 cells from duplicate flasks; **No Adverse Effects Indicated; Study Acceptable.** (Remsen (Gee) 12/17/85; Updated 5/8/89, Morgan)

DNA DAMAGE

** 50429-010; 36632; "Activity of FMC 54800 Technical (A83-980) in the Morphological Transformation of BALB/3T3 Mouse Embryo Cells in the Absence of Exogenous Metabolic Activation"; 844; Microbiological Associates, Bethesda, MD; 10/11/83; FMC 54800 Technical, Lot # E2392-105, purity = 88.35%; 0-100 µg/ml; 100 to 67% relative cloning efficiency; MNNG as positive control; no activation; no increase in transformation frequency by a.i. reported; **No Adverse Effects Indicated; Study Acceptable.** (Remsen (Gee) 12/17/85; Updated 5/9/89, Morgan)

50429-072; 44165; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes"; 844; Microbiological Associates, Bethesda, MD; 9/26/83; FMC 54800 Technical, Lot E-2392-105, 88.35%; 18 hour exposure; 0, 0.01, 0.05, 0.10, 0.50, 1.0 and 2.0 µl/ml; no consistent evidence for UDS. Study status changed over time, as follows. J. Remsen (Gee) originally reviewed and found study unacceptable but upgradeable with the submission of purity of test article, volume of medium used, size of plate, viability at start of test and explanation of "µl/ml" when test article was supplied as a solid (5/27/86). This study was reviewed again and found acceptable by Morgan on 5/19/89. Updated 8/31/89 by Morgan. It was determined in a subsequent review that the Net Grains/Nucleus for the control groups were too high to be considered usable, and the study was downgraded to unacceptable on 7/9/90, (Morgan and Gee).

50429-073; 44166; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes"; 844; Microbiological Associates, Bethesda, MD; 11/1/83; FMC 54800 Technical, Lot E-2392-105, purity = 88.35%; 0, 1.0, 1.5, 1.75, 2.0, 2.25 and 2.50 µl/ml; 18 hour exposure; no evidence for UDS; incomplete (missing data); **Study Unacceptable but upgradeable** with submission of initial viability of hepatocytes. (Gee 5/27/86, Updated 5/22/89, Morgan)

NEUROTOXICITY

** 50429-010; 36628; "The Acute Oral Toxicity (LD50) and Neurotoxic Effects of FMC 54800 Technical to the Domestic Hen"; 817; Huntingdon Research Centre, Huntingdon, England; 12/17/84; FMC 54800 Technical; 0, 500, 5000, 5000; 10 females/dose; Days 0-21; TOCP - positive control; Positive control - ataxia and neurotoxicity; Treated group - no evidence of acute delayed neurotoxicity; **No Adverse Effects Indicated; Study Acceptable.** (Remsen (Gee) 12/17/85; Updated 5/9/89, Morgan)

**50429-231 173399 , Watt, B. A., “FMC 54800 Technical: acute neurotoxicity screen in rats”, FMC Corporation Toxicology Laboratory, Princeton, NJ, 3/10/98. FMC Study No. A97-4643. Ten Sprague-Dawley CD rats/sex/group were dosed once by gavage with 0, 10, 35, or 75 mg/kg of FMC 54800 (bifenthrin) technical, 93.7% purity. Test article was administered undiluted, and corresponding negative controls were dosed with tap water at the same volume as the high dose rats. Design was consistent with guidelines for an acute rat neurotoxicity screening battery, including full FOB by technicians “blind” to treatment group, and motor activity measurements at pre-test, and on test days 0 (measurements timed to reflect peak anticipated responses), 7, and 14. At term of study, rats were

perfused with fixative, and tissues were prepared in paraffin (CNS and muscle samples) or plastic (peripheral nervous system structures). NOEL = 10 mg/kg (based on "tense" or "rigid" behavior of one mid-dose male during handling). Treatment-related findings in FOB were otherwise limited to 75 mg/kg males and females on Day 0. Signs included "tense" or "rigid" behavior, whole body tremors, abnormal posture, incoordination or ataxia, hindlimb splay, chromorhinorrhea, fur soiling, localized twitching, staggered gait, convulsions, "slight" to "severe" gait impairment, exaggerated auditory response, and uncoordinated righting reflex. Rarely were any of these findings evident in more than two rats per sex. Signs were generally limited to the day of dosing: none extended beyond one day after dosing. Study is **acceptable**, with **no adverse effects**. Aldous, 4/4/00.

50429-230 173398 Watt, B. A., "FMC 54800 Technical: subchronic neurotoxicity screen in rats", FMC Corporation Toxicology Laboratory, Princeton, NJ, 5/6/98. FMC Study # A97-4700. Ten Sprague-Dawley CD rats/sex/group were dosed in diet at 0, 50, 100, or 200 ppm of FMC 54800 (bifenthrin) technical, 93.7% purity for 13 weeks in a guideline subchronic neurotoxicity study. Design included full FOB by technicians "blind" to treatment group, and motor activity measurements at pre-test, and on test weeks 4, 8, and 13. At term of study, rats were perfused with fixative, and tissues were prepared in paraffin (CNS and muscle samples) or plastic (peripheral nervous system structures). Histopathology of controls and high dose rats found no treatment effects; hence intermediate groups were not examined. NOEL = 50 ppm (Males: 2.9 mg/kg/day; Females: 3.7 mg/kg/day), based on dose-related incidences of tremors or twitching, and decreases in forelimb and hindlimb grip strength. At week 4 in the open field observations, whole body tremors were seen in all high dose rats, and in all mid-dose females. By week 8, tremors were limited to 1/sex at the high dose, suggesting acquired tolerance. No tremors were noted at week 13. Forelimb and hindlimb grip strength was reduced in both sexes at 200 ppm at 4 weeks, and persisted in high dose females throughout the study. Further, hindlimb weakness was also evident in 100 ppm females at weeks 8 and 13. There were no motor activity effects. Study is **acceptable, with **no adverse effects**. Aldous, 4/4/00.

50429-229 173397 is the report of the 28-day range-finding study associated with Record No. 173398, above. The pilot study results justify the dose selection for the primary study. Aldous, 4/4/00 (noted in worksheet of the primary study).

PROPOSED FUTURE STUDIES

50429-167 149271 FMC proposed a rat dermal teratology study, using dose levels of 0, 5, 50, 100, and 300 mg/kg/day (above dose levels were stated in the summary, however the text on p. 4 gives proposed dose levels of 0, 10, 30, 100, and 300 mg/kg/day). This study was intended to replace the previously accepted rat **oral** teratology, which yielded a NOEL of 1 mg/kg/day, as the basis for an extrapolated (and unnecessarily conservative) estimate of a response pattern for the dermal route. As of 4/3/00, no study based on this design has been submitted. Aldous, 4/3/00.

50429-183 163504 Protocol for a study on "Oral/dermal bioavailability of bifenthrin". Purpose is to determine bioavailability of bifenthrin via iv, oral (gavage), and dermal routes. Protocol was dated 6/22/98. Aldous, 4/3/00.

50429-183 163505 Protocol for a study on "Twenty-one day repeated dose dermal toxicity study in

rats with Capture 2 EC". The range-finding study will test up to 4000 mg/kg/day of Capture 2EC, equivalent to 1000 mg/kg/day of bifenthrin technical. Aldous, 4/3/00.